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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/769,831	SCHWABE ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/17/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24 and 26-29* is/are pending in the application.

4a) Of the above claim(s) *13-19 and 21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,20,24 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *attached hereto* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed 3/17/08 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I and species of light detectable label in Applicant's response filed 7/5/07.

Claims 1-12, 20, 24 and 26-29 are currently being examined.

3. The Examiner notes that the Genbank database accession #1705995 disclosed by Applicant as SEQ ID NO: 23 at [0097] is Genbank database accession # P49747, version P49747 GI: 1705995 that encodes human cartilage oligomeric matrix protein precursor (COMP) (see evidentiary reference NCBI for Genbank Accession No. P49747).

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicant's said claim amendment in Applicant's response filed 3/17/08 has necessitated the following new rejection.

5. Claims 4 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed oligomeric MHC complex and pharmaceutical composition thereof, recited in the instant claims.

The instant claims encompass an oligomeric MHC complex wherein the oligomerising domain comprised in the second section of the at least three chimeric proteins is an oligomerizing domain from any cartilage oligomeric matrix protein (COMP) from any species. There is insufficient disclosure in the specification on such an oligomeric MHC complex and pharmaceutical composition thereof.

The specification discloses that the amino acid sequence of the oligomerisation domain for rat COMP is SEQ ID NO: 22, which corresponds to amino acid residues 20-83 of rat COMP ([0009]). The specification does not disclose the sequence of any other COMP protein from any other species except for human COMP at SEQ ID NO: 23 at [0097], the human sequence differing from the rat COMP pentamerization domain.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court held that disclosure of a single member of a genus (rat insulin) did not provide adequate written support for the claimed genus (all mammalian insulins) and also stated: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

As discussed above, the instant specification discloses the representative species of rat COMP and that amino acid residues 20-83 were capable of forming covalently linked pentamers (Discussion section of Effimov *et al*, incorporated by reference in its entirety in the instant specification). The instant specification further discloses Genbank database accession #1705995 is SEQ ID NO: 23 (see [0097] of the specification). Genbank database accession # P49747, version P49747 GI: 1705995, encodes human cartilage oligomeric matrix protein precursor (COMP) as noted above at item #3 of this Office Action. However, the specification discloses, in a prophetic manner, creating

HLA-A2 -β2m-COMP pentamers using amino acid residues 21-85 of 1705995, *i.e.,* there is no disclosure that the COMP region results in pentamer formation.

Although the instant specification has disclosed a domain of rat COMP that is capable of forming pentamers, the instant specification does not disclose a representative number of other species of other proteins that contain such regions that may form pentamers and are coiled-coil proteins. Nor does the specification identify which amino acid residues in the domain of rat COMP amino acid residues 20-83 are essential for preserving functional activity, *i.e.,* which homologous proteins or regions of proteins will retain the required activity.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the amendment filed 3/17/08 on pages 9-11.

Applicant has argued that the precise reasoning in this rejection is difficult to follow. However, Applicant and Examiner have discussed this rejection in an interview on 3/13/08. Applicant argues that a review of protein databases to compare COMP sequences of other species shows that COMP is not highly variant, and Applicant further presents an Appendix which content is the amino acid sequences of mouse, rat, human, bovine, horse and chimp like monkey COMP proteins, sequence alignment of rat with the other COMP amino acid residues 20-83, and a sequence identity matrix for COMP domains showing the degree of homology of these regions (the regions are 78% to 98% identical to rat, with all but the chimp sequence being known prior to Applicant's priority date). Applicant further argues "based on the high homology clearly evident, the practitioner of ordinary skill in the art would assume that these proteins have the same structure function. There are further no suggestions to the contrary in the literature, so far as is known."
However in response to Applicant's argument, evidentiary reference Whisstock *et al* (Quarterly Reviews of Biophysics 2003, 36(3): 307-340) teaches: "Prediction of protein function from sequence and structure is a difficult problem because homologous proteins often have different functions" (Abstract). Applicant further argues that Applicant has given the two examples of rat and human COMP that demonstrates that the structure function is conserved between human and rat COMP, and so it is therefore reasonable to assume that sequences from other mammalian species that have a higher homology [than 78%] with either human or rat COMP will also conserve the structure function of this core region. However, the specification has not disclosed the function for the protein designated as human COMP as enunciated in the instant rejection, and even if it did, homology is not necessarily consonant with function as evidenced by Whisstock *et al*. With regard to Applicant's further argument that even in the absence of other information, the claims are limited to COMP proteins that are

oligomer-forming coiled-coil proteins with an oligomerizing domain, thus clarifying the structure function requirement of these proteins in this regard, a definition by function does not suffice for written description purposes as enunciated above in the instant rejection.

6. For the purpose of prior art rejections, the filing date of the instant claim 26 is deemed to be the filing date of the instant application, *i.e.,* 2/2/04, as the parent applications have do not support the claim limitation: amino acid sequence of SEQ ID NO: 22.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-12, 20, 26, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/21572 A1(of record) in view of WO 98/18943 A1 (of record), Terskikh *et al* (PNAS USA 1997, 94:1663-1668, IDS reference), Muller *et al* (Meth. Enzymol. 2000, 326, pages 261-282, IDS reference), Efimov *et al* (FEBS Letters, 1994, 341: 54-48, of record) and Efimov *et al* (Proteins 1996, 24: 259-262, of record).

This new rejection is necessitated by Applicant's addition of new claims 28 and 19. The Examiner notes that claims 1-12, 20 and 26 were previously rejected upon the grounds enunciated below in the prior rejection of record.

WO 99/21572 A1 teaches oligomeric MHC single chain (sc) class I or class II complexes comprising a first portion consisting of one or more single chain class I or class II linked or fused to a joining molecule and optionally an effector molecule, said joining molecule linking the first portion to a second such portion, said joining molecule can be a peptide tag, an IgH or IgL chain, or a coiled-coil domain. WO 99/21572 A1 further teaches that single chains of MHC can be combined to produce novel homo-or-heterodimeric MHC complexes (page 8 at the first paragraph) and further teaches that the number of linked molecules will generally be between about 2 to 10 (first paragraph

on page 31). WO 99/21572 A1 teaches that the effector molecule can be an scFv antibody, said scFv antibody specific for the same TCR the MHC molecule is specific for or for a different molecule. WO 99/21572 A1 further teaches that the complex may comprise a label such as a radionuclide, and the sc MHC molecule may be linked to an antigenic peptide that binds in the MHC binding groove, *e.g.*, an immunodominant peptide from MBP, type II collagen, GAD for which a T cell response exists in a patient. WO 99/21572 A1 teaches pharmaceutical compositions comprising the oligomeric MHC class II complexes (see entire reference, especially page 3 at the last paragraph, paragraph spanning pages 4-5, page 30 at lines 4-33, page 31, page 32 through line 32, page 42 at lines 11-13 and lines 22-34, page 51 at lines 6-22, page 52 at lines 8-12, figure 9, figure 10).

WO 99/21572 A1 does not teach wherein the coiled-coil domain is the COMP pentamerization domain(s) recited in the instant claims.

WO 98/18943 A1 teaches that small peptides can be pentamerized using the pentamerization domain of COMP (a coiled-coil) with or without a linker. WO 98/18943 A1 teaches that the domain capable of binding to an acceptor and the construct may further comprise a domain such as a marker or an enzyme or a binding domain, and the said acceptor is for example a receptor. WO 98/18943 A1 teaches that the COMP assembly domain spontaneously pentamerizes *in vitro* or *in vivo*, and since it does not depend upon disulfide bond formation, is therefore a preferred embodiment of the invention. WO 98/18943 A1 teaches that oligomerization of short peptides bypasses folding problems and overcomes expression difficulties previously experienced during oligomerization of relatively complex proteins such as scFV fragments (see entire reference, especially page 2 at the detailed description of the invention, page 3 at the second and third full paragraphs, page 4 at the first two paragraphs, page 5 at the first two full paragraphs, claims).

Terskikh *et al* teach a pentameric peptabody comprising the pentamerization domain of COMP, a coiled-coil assembly domain. Terskikh *et al* teach that the COMP assembly domain spontaneously forms a five-stranded α helical bundle, the highest oligomerization state known for a compact coiled-coil structure. Terskikh *et al* teach that various forms of this domain can be readily produced in *E. coli* and easily purified to near homogeneity under nondenaturing conditions. "These properties, taken together with a remarkable solubility in salt-free water (up to 20 mg/ml) and thermostability, make the COMP assembly domain an ideal pentamerization tool for protein engineering…thus….bypasses the difficulties previously encountered during the expression of oligomeric forms of relatively complex proteins, such as single chain Fv fragments". Terskikh *et al* teach that the fusion of the protein-COMP construct to other different relevant polypeptides such as an FcR binding domain, would provide new functional properties to this molecule in addition to the multivalent high avidity binding (especially abstract, Introduction, first paragraph at column 1 on page 1664, discussion section).

Muller *et al* teach that chimeric multimers made by genetic fusions to heterologous oligomerization domains can be constructed with coiled coils that act as versatile fusion partners, having small domains with predictable quaternary structure and adjustable stability (especially first paragraph). Muller *et al* teach that the best-characterized pentamer occurs in COMP (especially page 264, last sentence at the end of the first full paragraph). Muller *et al* teach using coiled coils to generate chimeric proteins with higher avidity (especially paragraph spanning pages 267-269). Muller *et al* teach that the coiled coil can be genetically fused to the protein of interest via a flexible linker (especially first sentence on page 269). Muller *et al* teach fusion of scFv to the N terminus of a coiled coil leads to association of scFv fragments according to the oligomerization state of the coiled coil, and a tetrameric scFv molecule (second full paragraph on page 276). Muller *et al* teach adding fluorescent labels to the multimers, and use of the multimers for numerous biochemical, genetic, diagnostic and therapeutic applications (especially page 281 at the last two paragraphs).

Efimov *et al* (1994) teach that amino acid residues 20-83 of COMP protein can be over-expressed in *E. coli* and purified under non-denaturing conditions. Efimov *et al* teach that this fragment forms pentamers similar to the assembly domain of the native protein, and its five chains can be covalently linked *in vitro* by oxidation of cysteines 68 and 71. Efimov *et al* teach that this fragment adopts a predominantly α-helical structure as judged by circular dichroism spectroscopy (especially abstract).

Efimov *et al* (1996) teach that COMP is a pentameric glycoprotein and that self-association of COMP is achieved through the formation of a five-stranded α-helical bundle that involves amino acid residues 20-83, and the further stabilization by interchain disulfide bonds between cysteines 68 and 71. Efimov *et al* (1996) teach that COMP assembly domain has features of a coiled-coil (especially abstract and introduction section).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used as the coiled-coil domain, in the MHC-linker-coiled-coil-scFV oligomeric construct taught by WO 99/21572 A1, the coiled-coil COMP assembly domain taught by WO 98/18943 A1, Terskikh *et al*, Muller *et al*, Efimov *et al* (1994) and Efimov *et al* (1996). It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the contruct taught by WO 99/21572 A1 without the scFv since WO 99/21572 A1 teaches the scFv effector molecule is optional.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to create a higher avidity MHC multimer because WO 99/21572 A1 teaches an MHC oligomeric complex containing coiled-coil domains and the advantages of using them to increase avidity of MHC complexes, Terskikh *et al* teach that the COMP assembly domain spontaneously forms a five-stranded α helical bundle, the highest oligomerization state known for a compact coiled-coil structure, and

this domain can be readily produced in *E. coli* and easily purified to near homogeneity under non-denaturing conditions, and use of such domain can bypass problems encountered in the expression of oligomerized forms of relatively complex proteins, Muller *et al* teach the versatility and stability of coiled-coil domains for oligomerizing proteins, the advantage of increased avidity that their use provides, and their use in various diagnostic and therapeutic applications, Efimov *et al* (1994) teach that amino acid residues 20-83 of COMP protein can be over-expressed in *E. coli* and purified under non-denaturing conditions, Efimov *et al* (1996) teach the location of the COMP assembly domain, that it spontaneously forms a pentameric structure and is a coiled-coil domain.

Applicant's arguments in the amendment filed 3/17/08 have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the said amendment on pages 11-19.

With respect to the said arguments the following applies.

Applicant is arguing the references separately. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed.Cir.1986).

Furthermore, the primary reference WO 99/21572 A1 teaches oligomeric complexes of about 2 to 10 linked molecules each comprising a scMHC class I or class II molecule linked or fused to a joining molecule that is a coiled coil and optionally, the coiled coil is linked or fused to an effector molecule such as an scFv protein. Secondary references WO 98/18943 A1 and Terskikh *et al* teach pentamerization of peptides using the COMP pentamerization domain, and both teach that that oligomerization of short peptides bypasses folding problems and overcomes expression difficulties previously experienced during oligomerization of relatively complex proteins such as scFV fragments. Yet secondary reference Muller *et al* teach fusion of scFv to the N terminus of a coiled coil leads to association of scFv fragments according to the oligomerization state of the coiled coil, and the successful production of a functional tetrameric scFv-coiled coil molecule, indicating that the prior folding problems and expression difficulties of the complex protein scFv were overcome, and further include teaching selection of an appropriate linker between the scFv and the coiled coil domain in order to preserve functionality of the scFv. Muller *et al* also teach that "certain properties of fusion proteins that can restrict the efficacy of such chimeras should be addressed at an early stage. For scFv fragments that tended to aggregate, bringing together two or more molecules resulted in poor to very poor yields. Solving this problem required improving the folding efficiency of the scFv and developing effective purification methods...In general, when the components of hetero-oligomers are unstable in isolation,

coexpression is likely to reduce aggregation due to prolonged exposure of hydrophobic surfaces and degradation of partially folded domains", indicating that the art recognizes that problems encountered in the production of complex proteins as well as the hetero-oligomers formed with these proteins and an oligomerizing domain have art-recognized methods of improving yield and production, respectively.

A further reading past the cited teaching by Applicant in Muller *et al* (*i.e.,* that the versatility of coiled coils for oligomerization derives from their diversity of oligomeric structure, page 261), reveals that the different properties of the oligomerizing domains result in different degrees of the said domains to oligomerize, *i.e.,* to form trimers, tetramers, decamers, *etc.* The said teaching does not, in contrast to Applicant's assertion, amount to a teaching that this diversity in property would make the outcome of an attempt to fuse any particular type of coiled coil to any other particular category of protein inherently uncertain. Applicant argues that Muller *et al* teach (on page 267) that the most straightforward application of coiled coil fusions is replacement of natural oligomerization domains, and provides examples of such. However, said teaching does not preclude that coiled coil fusions may not be used in other instances, and as is evidenced by the successful construction of scFv coiled coil tetrameric complexes. Applicant further argues that scFv fragments are much more likely to refold on their own than MHC molecules since they are intrinsically smaller and substantially less complex in structure than MHC molecules. However, Applicant does not present evidence, and in fact, the prior filed (7/5/07) Rule 1.132 Declaration of Gerald T. Nepom, at item 4 admits that immunoglobulin variable domains are structurally similar in size and orientation to the MHC domains which are used in the multimers. The Examiner notes that scMHC class I is about 57 kDa, scMHC class II is about 60 kDa (these molecular masses are for class I and class II in glycosylated form, but in non-glycosylated form produced in *E. coli*, the molecular mass would be expected to be smaller for each), and scFv is about 42 kDa, the same approximate size. In addition, as discussed supra, the art considers scFv to be a complex protein.

Applicant argues that MHC molecules assemble under conditions that are different from the conditions under which COMP assembles (Applicant does not provide evidence or explanation for what these conditions are), that there are no examples in the prior art for fusion proteins that have been achieved with COMP, and that the key difference of the MHC molecule is that its subunits are not very stable on their own and it can be expected that they will aggregate when fused to other hydrophobic binding partners. However, in Applicant's prophetic example in the instant specification, the components of the complex are co-expressed using art recognized methods for producing MHC class I complexes.

Applicant cites the J. Immunological Methods 2002, Vol. 268, No. 1, entire issue for the teaching of MHC tetramer technology which was the dominant MHC oligomer technology at the time. Applicant argues that to Applicant's knowledge, the example of

WO 99/21572 of creating a fusion protein with a dimeric leucine zipper to generate MHC dimers has never actually been put into practice.

However, that the art references do not exemplify fusion proteins with COMP does not overcome the instant rejection based upon the combined references. To reiterate a prior point, the art cited supra in this rejection teaches coexpression of the components of the oligomer is likely to reduce aggregation due to prolonged exposure of hydrophobic surfaces and degradation of partially folded domains", indicating that the art recognizes that problems encountered in the production of complex proteins as well as the hetero-oligomers formed with these proteins and an oligomerizing domain have art-recognized methods of improving yield and production, respectively, and in particular to the problem of scFv. The J. Immunological Methods 2002, Vol. 268, No. 1 discussed by Applicant is not of record. In response to Applicant's arguments to dimeric leucine zipper/MHC dimers never being produced, US 2005/0003431 A1 (with priority to at least 2/12/99) exemplifies production of an MHC class II dimeric leucine zipper (Examples). Leucine zippers are also hydrophobic molecules. In addition, the prior filed (7/5/05) said Declaration under 1.132 states that a person of ordinary skill in the art would have been sufficiently skilled and aware of techniques to produce MHC dimers or tetramers using a variety of scaffold components, including leucine zippers.
Applicant further argues that section 11 of the said J. Immunological Methods concludes that the standard MHC tetramers are now so popular that it is difficult for other multivalent reagents to compete. Applicant argues that since then, the MHC pentamer technology of the instant application has become the only other MHC multimer technology which has been able to successfully compete with and improve on MHC tetramers, that use of the Pro5^{TM} MHC pentamers is now published at twice rate in scientific publications as the use of MHC tetramers from the strongest competitor Beckman Coulter, Inc, is also a multiple of that of any other MHC oligomer technology, and that no functional MHC oligomers that rely on use of a coiled-coil domain for oligomerisation other than Pro5^{TM} MHC pentamers have ever been published, so far as if known.

However, the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the authors of the prior art derived the disclosed subject matter from the Applicant. MPEP 716.01(a). Applicant who is asserting commercial success to support its contention of nonobviousness bears the burden of proof of establishing a nexus between the claimed invention and evidence of commercial success. MPEP 716.03.

For these reasons and for the reasons enunciated in the instant rejection, one of ordinary skill in the art would have had a reasonable expectation of success in combining the cited references to produce the claimed invention.

10. Claims 24 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/21572 A1 in view of WO 98/18943 A1 (of record), Terskikh *et al* (PNAS USA 1997, 94:1663-1668, IDS reference), Muller *et al* (Meth. Enzymol. 2000, 326, pages 261-282, IDS reference), Efimov *et al* (FEBS Letters, 1994, 341: 54-48, of record) and Efimov *et al* (Proteins 1996, 24: 259-262, of record) as applied to claims 1-12, 20, 26, 28 and 29 above, and further in view of Dinser *et al* (J. Clin. Invest. 8/15/02,110(4): 505-513, of record), Newton *et al* (Genomics. 1994, 24: 435-439, of record) and admissions in the instant specification at [0097]-[0098].

WO 99/21572, WO 98/18943 A1, Terskikh *et al* (PNAS USA 1997, 94:1663-1668, IDS reference), Muller *et al* (Meth. Enzymol. 2000, 326, pages 261-282, IDS reference), Efimov *et al* (FEBS Letters, 1994, 341: 54-48, of record) and Efimov *et al* (Proteins 1996, 24: 259-262, of record) have all been discussed supra, hereafter referred to as "the combined references."

The combined references do not teach using an oligomerizing domain that is derived from the pentamerization domain of human COMP recited in instant claim 27, including one comprising the amino acid residues recited in instant claim 24.
Dinser *et al* teach that human COMP consists of an N-terminal coiled-coil domain followed by several other domains, and that its sequence was known (especially paragraph spanning columns 1-2 on page 505 and reference 17 in the bibliography).

Newton *et al* teach cloning and sequencing of human COMP, and the region that is required for pentamer formation (especially abstract and Figure 2).

The admissions in the instant specification at [0097]-[0098] are that SEQ ID NO: 23 is Genbank accession #1705995 (human COMP) and that SEQ ID NO: 24 is amino acid residues 21-87 of SEQ ID NO: 23, respectively.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have constructed the MHC class I or class II oligomeric complexes taught by the combined references by substituting the rat COMP coiled-coil domain taught by the combined references with the human COMP coiled-coil domain taught by Dinser *et al* and by Newton *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a less immunogenic construct for a pharmaceutical composition intended for humans, as the combined references, particularly WO 99/21572 A1, teach that the constructs may be made with human class I or class II MHC molecules (paragraph spanning pages 49-50), and Dinser *et al* and Newton *et al* teach the corresponding human COMP coiled-coil domain region.

Applicant's arguments in the amendment filed 3/17/08 have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the said amendment on page 20.

The Examiner's response to Applicant's arguments at item #10 supra apply herein.

11. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/070725 A1 (of record) in view of WO 99/21572 A1 (of record).

WO 02/070725 A1 teaches that the multimerization domain of COMP or TSP-5 is a coiled coil domain and can be used to make a chimeric protein of the invention. WO 02/070725 A1 teaches that such conjugates can be made by a conjugation of the multimerization domain of COMP and any protein or amino acid drug, including ones derived from human proteins (especially paragraph spanning pages 15-16, page 16 at the first full paragraph). WO 02/070725 A1 teaches that the chimeric proteins can have the structure of the pentamers comprising the multimerization domain of human COMP, a spacer, and a protein or amino acid drug or pentamers comprising a specific amino acid domain to a specific site of action, a spacer, the multimerization domain of human COMP, a spacer and a protein or amino acid drug, and wherein the chimeric protein arms of different types are joined at the COMP multimerization domain. WO 02/070725 A1 teaches that the multimerization domain of COMP is amino acid residues 1-88 (especially Examples III and IV, claims and figures).

WO 02/070725 A1 does not teach wherein the COMP is the coiled-coil domain in an MHC oligomeric complex.

WO 99/21572 A1 teaches oligomeric MHC single chain (sc) class I or class II complexes comprising a first portion consisting of one or more single chain class I or class II linked or fused to a joining molecule and optionally an effector molecule, said joining molecule linking the first portion to a second such portion, said joining molecule can be a peptide tag, an IgH or IgL chain, or a coiled-coil domain. WO 99/21572 A1 further teaches that single chains of MHC can be combined to produce novel homo-or-heterodimeric MHC complexes (page 8 at the first paragraph). WO 99/21572 A1 teaches that the effector molecule can be an scFv antibody, said scFv antibody specific for the same TCR the MHC molecule is specific for or for a different molecule. WO 99/21572 A1 further teaches that the complex may comprise a label such as a radionuclide, and the sc MHC molecule may be linked to an antigenic peptide that binds in the MHC binding groove, *e.g.,* an immunodominant peptide from MBP, type II collagen, GAD for which a T cell response exists in a patient. WO 99/21572 A1 teaches pharmaceutical compositions comprising the oligomeric MHC complexes (see entire reference, especially page 3 at the last paragraph, paragraph spanning pages 4-5, page 30 at lines 4-33, page 31, page 32 through line 32, page 42 at lines 11-13 and lines 22-34, page 51 at lines 6-22, page 52 at lines 8-12, figure 9, figure 10).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have constructed an oligomeric protein complex such as taught by WO 02/070725 A1 comprising the human COMP pentamerization domain taught by WO 02/070725 A1, including the MHC class I or class II complexes or chains taught by WO 99/21572 A1 and optionally also including an scFv antibody as taught for the oligomeric coiled-coil complexes of WO 99/21572 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 02/070725 A1 teaches that the multimerization domain of COMP or TSP-5 is a coiled coil domain that can be used to make a chimeric protein containing one or two protein or peptide drugs or specific amino acid domains to specific sites of action, and WO 99/21572 A1 teaches MHC class I or class II coiled-coil multimers, optionally also containing scFv effectors, and their usefulness as pharmaceuticals.

Applicant's arguments in the amendment filed 3/17/08 have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the said amendment on page 20.
The Examiner's response to Applicant's arguments at item #10 supra apply herein.

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-12, 20, 24 and 26-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-26 and 29 of copending Application No. 10/770,140. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '140 are encompassed by the instant claims.

Applicant's arguments in the amendment filed 3/17/08 have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the said amendment on pages 20-21, briefly, that Applicant does not at this time concede that the claims of the respective applications are patentably indistinct; however, the present application and '140 were both filed in the U.S. on the same day, *i.e.*, 2/2/04, and since they were co-filed, the present application should be considered the base application for co-filed patent in accordance with MPEP 804(I)(B)(1), and the rejection withdrawn to allow the present application to issue without a requirement for a terminal disclaimer.
The Examiner notes Applicant's remarks, however, at this time, the rejection stands.

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Group 1640
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June 19, 2008

/G.R. Ewoldt/
Primary Examiner, Art Unit 1644